(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 738 512 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
23.10.1996 Bulletin 1996/43

(21) Application number: **96106104.1**

(22) Date of filing: **18.04.1996**

(51) Int. Cl.[6]: **A61K 31/365**, A61K 31/22, A61K 31/415, A61K 31/66, A61K 31/405, A61K 31/40

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **19.04.1995 US 424984**

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(54) Use of a HMG CoA reductase inhibitor to prevent a second heart attack

(57) A method is provided for preventing or reducing the risk of a second heart attack in a patient having a substantially normal serum cholesterol level by administering an HMG CoA reductase inhibitor such as pravastatin, alone or in combination with an ACE inhibitor.

EP 0 738 512 A1

Printed by Rank Xerox (UK) Business Services
2.13.8/3.4

Description

The present invention relates to the use of an HMG CoA reductase inhibitor, such as pravastatin, alone or in combination with an ACE inhibitor for the preparation of a pharmaceutical composition suitable for preventing or reducing the risk of a second heart attack in a patient having a substantially normal cholesterol level.

In accordance with the present invention, a method is provided for preventing onset of or reducing risk of a second heart attack in a mammalian species having a substantially normal serum cholesterol level, wherein a therapeutically effective amount of an HMG CoA reductase inhibitor, alone or in combination with an ACE inhibitor, is administered to a mammalian species having a substantially normal serum cholesterol level systemically, such as orally or parenterally.

In preferred embodiments where the patient to be treated in accordance with the present invention is normotensive, the angiotensin converting enzyme inhibitor, where employed, will preferably be administered in amounts below that required to cause hemodynamic effects, that is below that required to cause a reduction in blood pressure.

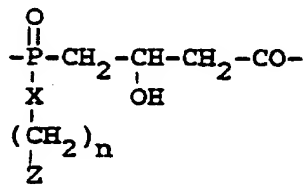
The combination of the HMG CoA reductase inhibitor and ACE inhibitor will be employed in a weight ratio to each other of within the range of from about 0.001:1 to about 1000:1 and preferably from about 0.05:1 to about 100:1.

The HMG CoA reductase inhibitor, alone or in combination with the ACE inhibitor will be administered as soon as possible after the initial myocardial infarction.

The term "substantially normal serum cholesterol level(s)" refers to a total cholesterol (TC) of less than 200 mg/dl, and preferably less than 190 mg/dl.

The HMG CoA reductase inhibitors suitable for use herein include, but are not limited to, mevastatin and related compounds as disclosed in US-A-3,983,140, lovastatin (mevinolin) and related compounds as disclosed in US-A-4,231,938, pravastatin and related compounds such as disclosed in US-A-4,346,227, velostatin (synvinolin) and related compounds as disclosed in US-A-4,448,784 and US-A-4,450,171, with lovastatin, pravastatin or velostatin being preferred. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluindostatin (Sandoz XU-62-320), pyrazole analogs of mevalonolactone derivatives as disclosed in US-A-4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)alkyl]-pyran-2-ones and derivatives thereof as disclosed in US-A-4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in FR-B-2,596,393, 2,3-di-substituted pyrrole, furan and thiophene derivatives as disclosed in EP-A-0221025, naphthyl analogs of mevalonolactone as disclosed in US-A-4,686,237, octahydro-naphthalenes such as disclosed in US-A-4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in EP-A-0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837 which compounds have the moiety



wherein X is -O- or -NH-, n is 1 or 2 and Z is a hydrophobic anchor.

Examples of such compounds include (S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]-methoxy]methoxyphosphinyl]-3-hydroxy-butanoic acid, methyl ester or its monolithium salt,

(S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methoxy]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt,

(3S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methoxy]methylphosphinyl]-3-hydroxybutanoic acid, monolithium salt,

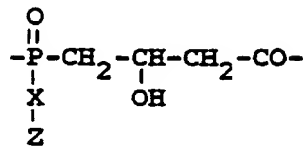
(S)-4-[[[2,4-dichloro-6-[(4-fluorophenyl)-methoxy]phenyl]methoxy]methoxyphosphinyl]-3-hydroxybutanoic acid, monolithium salt,

(3S)-4-[[[2,4-dichloro-6-[(4-fluorophenyl)-methoxy]phenyl]methoxy]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt,

(3S)-4-[[[2,4-dichloro-6-[(4-fluorophenyl)-methoxy]phenyl]methoxy]methylphosphinyl]-3-hydroxybutanoic acid, or its methyl ester, and

(S)-4-[[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methyl]amino]methoxyphosphinyl]-3-hydroxybutanoic aicd, monolithium salt.

Another class of HMG CoA reductase inhibitors suitable for use herein include phosphinic acid compounds disclosed in GB 2205838, which compounds have the moiety



wherein X is $-CH_2-$, $-CH_2-CH_2-$, -CH=CH-, $-CH_2CH_2CH_2-$, -C=C- or $-CH_2O-$, where O is linked to Z, and Z is a hydrophobic anchor.

Examples of such compounds include (S)-4-[[[1-(4-fluorophenyl)-3-(1-methylethyl)-1H-indol-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxyfutanoic acid, or its sodium salt (SQ 33,600) (preferred) or its dilithium salt;

(S)-4-[[(E)-2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt;
(S)-4-[[2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, methyl ester or mono- or di-alkali metal salts thereof;
(S)-4-[[[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethynyl]methoxyphosphinyl]- 3-hydroxybutanoic acid or the methyl ester thereof;
(5Z)-4-[[2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, methyl esters thereof;
(S)-4-[[2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl esters;
(S)-4-[[2-[[1,1'-biphenyl]-2-yl]ethyl]-methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(SZ)-4-[[2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[[1,1'-biphenyl]-2-yl]ethyl]-hydroxyphosphinyl]-3-butanoic acid, dilithium salt;
(S)-4-(hydroxymethoxyphosphinyl)-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butanoic acid, methyl ester, or its dicyclohexylamine (1:1) salt;
(S)-4-[[2-[1-(4-fluorophenyl)-3-(1-methylethyl)-1-indol-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or disodium salt or methyl ester thereof;
(E)-4-[[2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(E)-4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[[2,4-dimethyl-6-[(4-fluorophenyl)-methoxy]phenyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[[2,4-dimethyl-6-[(4-fluorophenyl)-methoxy]phenyl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[2-[3,5-dimethyl[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[2-[4'-fluoro-3,5-dimethyl[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[2-[[1,1'-biphenyl]-2-yl]ethynyl]-hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]methoxy phosphinyl]-3-hydroxybutanoic acid, methyl ester;

(S)-4-[[2-[1-(4-fluorophenyl)-3-(1-methylethyl)-1H-indol-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(E)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethenyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(E)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]hydroxy phosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazole-5-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazole-5-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazol-5-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazol-5-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[[2-(cyclohexylmethyl)-4,6-dimethylphenyl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
4-[[2-[2-(cyclohexylmethyl)-4,6-dimethylphenyl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[2-[2-(cyclohexylmethyl)-4,6-dimethylphenyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
4-[[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]oxy]methyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[[1-(4-fluorophenyl)-3-methyl-2-naphthalenyl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(E)-4-[[2-[1-(4-fluorophenyl)-3-methyl-2-naphthalenyl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[2-[1-(4-fluorophenyl)-3-methyl-2-naphthalenyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
4-[[3-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]propyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
4-[[3-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]propyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
[1S-[1α(R*),2α,4αβ,8β,8aα]]-4-[[2-[8-(2,2-dimethyl-1-oxobutoxy)decahydro-2-methyl-1-naphthalenyl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
[1S-[1α(R*),2α,4αβ,8β,8aβ]]-4-[[2-[8-(2,2-dimethyl-1-oxobutoxy)decahydro-2-methyl-1-naphthalenyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

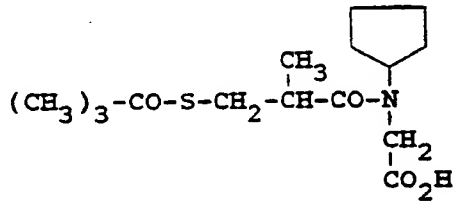
(S)-4-[[[[3'-(4-fluorophenyl)spiro]cyclopentane-1,1'-[1H]indene]-2-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester; and

(S)-4-[[[[3'-(4-fluorophenyl)spiro]cyclopentane-1,1'-[1H]indene]-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt.

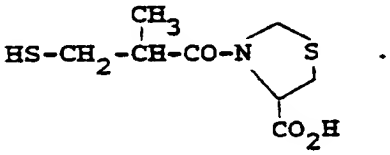
Preferred are pravastatin or SQ 33,600.

The angiotensin converting enzyme inhibitor which may be employed herein preferably includes those containing a mercapto (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in US-A-4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, being preferred, and mercaptoacyl derivatives of substituted prolines such as any of those disclosed in US-A-4,316,906 with zofenopril being preferred.

Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril, that is



and YS980, that is



Other examples of angiotensin converting enzyme inhibitors which may be employed herein include any of those disclosed in US-A-No. 4,374,829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred, any of the phosphonate substituted amino or imino acids or salts disclosed in US-A-4,452,790 with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)-phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29,852 or ceranapril) being preferred, phosphinylalkanoyl prolines disclosed in US-A-4,168,267 mentioned above with fosinopril being preferred, any of the phosphinylalkanoyl substituted prolines disclosed in US-A-4,337,201, and the phosphonamidates disclosed in US-A-4,432,971 discussed above.

Other examples of ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as disclosed in EP-B-80822 and EP-B-60668; Chugai's MC-838 disclosed in CA. 102:72588v and Jap. J. Pharmacol. 40:373 (1986); Ciba-Geigy's CGS 14824 (3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed GB 2103614 and CGS 16,617 (3(S)-[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in US-A-4,473,575; cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in EP-B-79-022 and Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) disclosed in Arzneimittelforschung 35:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987); R_o 31-2201 (Hoffman-LaRoche) disclosed in FEBS Lett. 165:201 (1984); lisinopril (Merck) disclosed in Curr. Therap. Res. 37:342 (1985) and EP-B-12-401, indalapril (delapril) disclosed in US-A-4,385,051; indolapril (Schering) disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983); spirapril (Schering) disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5):173 (1986); perindopril (Servier) disclosed in Eur. J. Clin. Pharmacol. 31:519 (1987); quinapril (Warner-Lambert) disclosed in US-A-4,344,949 and CI 925 (Warner-Lambert) ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinoline-carboxylic acid HCl) disclosed in Pharmacologist 26:243, 266 (1984), WY-44221 (Wyeth) disclosed in J. Med. Chem. 26:394 (1983).

Preferred are those ACE inhibitors which are proline or substituted proline derivatives and most preferred are such ACE inhibitors which include a mercapto group.

In carrying out the method of the present invention, the HMG CoA reductase inhibitor alone or in combination with the ACE inhibitor may be administered to mammalian species having substantially normal serum cholesterol levels, such as dogs, cats, humans, etc., and as such may be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid of sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

Thus, for oral administration, a satisfactory result may be obtained employing the HMG CoA reductase inhibitor in dosages employed, for example, for pravastatin, lovastatin and simvastatin as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount of from about 0.5 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

With regard to the ACE inhibitor, for oral administration, a satisfactory result may be obtained employing the ACE inhibitor in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 5 mg/kg.

A preferred oral dosage form , such as tablets or capsules, will contain the ACE inhibitor in an amount of from about 0.1 to about 500 mg, preferably from about 2 to about 50 mg, and more preferably from about 10 to about 25 mg.

For parenteral administration, the ACE inhibitor will be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 2 mg/kg.

The HMG CoA reductase inhibitor and ACE inhibitor may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

Tablets of various sizes can be prepared, e.g., of about 2 to 2000 mg in total weight, containing one or both of the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier of other materials according to accepted pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending one or the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

Liquid formulations can also be prepared by dissolving or suspending one or the combination of the active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

According to another modification, in order to more finely regulate the dosage schedule, the active substances may be administered separately in individual dosage units at the same time or carefully coordinated times. Since blood levels are built up and maintained by a regulated schedule of administration, the same result is achieved by the simultaneous presence of the two substances. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

Fixed combinations of HMG CoA reductase inhibitor and ACE inhibitor are more convenient and are preferred, especially in tablet or capsule form for oral administration.

In formulating the compositions, the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup of elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

Some of the active substances described: above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The formulations as described above will be administered for a prolonged period, that is, for as long as the potential for a second heart attack remains or the symptoms continue. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed. A dosing period of at least one to two weeks are required to achieve minimal benefit.

The following Examples represent preferred embodiments of the invention.

Example 1

A pravastatin formulation in the form of tablets having the following composition was prepared as described below.

Ingredient	Parts by Weight
Pravastatin	7
Lactose	67
Microcrystalline cellulose	20
Croscarmellose sodium	2
Magnesium stearate	1
Magnesium oxide	3

Pravastatin, magnesium oxide and a fraction (30%) of the lactose were mixed together for 2 to 10 minutes employing a suitable mixer. The resulting mixture was passed through a #12 to #40 mesh size screen. Microcrystalline cellulose, croscarmellose sodium and the remaining lactose were added and the mixture was mixed for 2 to 10 minutes. Thereafter, magnesium stearate was added and mixing was continued for 1 to 3 minutes.

The resulting homogeneous mixture was then compressed into tablets each containing 5 mg, 10 m, 20 mg or 40 mg pravastatin which may be used in preventing or reducing risk of a second heart attack in a patient having a substantially normal serum cholesterol level.

Example 2

Pravastatin tablets are prepared employing conmventional pharmaceutical techniques containing 20 mg pravastatin and inert ingredients employed in lovastatin tablets, namely cellulose, color, lactose, magnesium stearate and starch and butylated hydroxyanisole as a preservative as described in the 1990 Physician's Desk Reference (PDR).

The pravastatin tablets may be employed to prevent or reduce risk of a second heart attack in a patient having a substantially normal serum cholesterol level in accordance with the present invention.

Example 3

Tablets of the following compositions are prepared as described below.

Ingredient	Weight (mg)
SQ 33,600	100 mg
Avicel	112.5 mg
Lactose	113 mg
Cornstarch	17.5 mg
Stearic Acid	7 mg
	350 mg

The tablets are prepared from sufficient bulk quantities by slugging the SQ 33,600, Avicel, and a portion of the stearic acid. The slugs are ground and passed through a #2 screen and then mixed with the lactose, cornstarch, and the remainder of stearic acid. The mixture is compressed into 350 mg capsule shaped tablets in a tablet press. The tablets are scored for dividing in half.

The so-formed tablets may be administered in accordance with the teachings of the present invention to prevent or reduce risk of a second heart attack in a patient having a substantially normal serum cholesterol level.

Example 4

Lovastatin tablets are prepared employing conventional pharmaceutical techniques containing 20 mg lovastatin, cellulose, color, lactose, magnesium stearate and starch and butylated hydroxyanisole as a preservative as described in the 1990 PDR.

The lovastatin tablets may be employed to prevent or reduce risk of second heart attack in a patient having a substantially normal serum cholesterol level in accordance with the present invention.

Example 5

A pravastatin formulation in the form of tablets is prepared as described in Example 1.

A captopril formulation suitable for oral administration together with pravastatin is prepared as described below.

1000 tablets each containing 25 mg of 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline were produced from the following ingredients.

1-[(2S)-3-Mercapto-2-methylpropionyl]-L-proline (captopril)	25 g
Corn starch	50 g
Gelatin	7.5 g
Avicel (microcrystalline cellulose)	25 g
Magnesium stearate	2.5 g

The captopril and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet to form 1000 tablets each containing 25 mg of active ingredient.

The pravastatin tablets and captopril tablets may be administered as a combination in accordance with the teachings of the present invention to prevent or reduce the risk of a second heart attack in a patient having a substantially normal serum cholesterol level. In addition, the pravastatin and captopril tablets may be ground up into powders and used together in a single capsule.

Example 6

Pravastatin tablets are prepared as described in Example 2.

The pravastatin tablets may be employed in combination with enalapril tablets containing 20 mg enalapril and inactive ingredients as described in the 1990 PDR, in separate or combined dosage forms to prevent or reduce the risk of a second heart attack in a patient having a substantially normal serum cholesterol level in accordance with the present invention.

Example 7

Tablets containing SQ33,600 prepared as described in Example 3 may be administered together with 25 mg captopril tablets to prevent or reduce risk of a second heart attack in a patient having a substantially normal serum cholesterol level.

Example 8

Lovastatin tablets are prepared employing conventional pharmaceutical techniques containing 20 mg lovastatin, cellulose, color, lactose, magnesium stearate and starch and butylated hydroxyanisole as a preservative as described in the 1990 PDR.

The lovastatin tablets may be employed alone or in combination with the captopril tablets (described in Example 5) or ceranapril tablets in separate or combined dosage forms to prevent or reduce risk of a second heart attack in a patient having a substantially normal serum cholesterol level in accordance with the present invention.

Claims

1. Use of an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase alone or in simultaneous or separate sequential combination with an angiotensin converting enzyme (ACE) inhibitor for the preparation of pharmaceutical compositions suitable for preventing or reducing the risk of a second heart attack in a mammalian species having a substantially normal serum cholesterol level.

2. Use according to Claim 1 wherein said inhibitor of the enzyme HMG CoA reductase is mevastatin, lovastatin, pravastatin or velostatin.

3. Use according to Claim 1 wherein said inhibitor of the enzyme HMG CoA reductase is a pyrazole analog of a mevalonolactone, an indene analog of mevalonolactone, a 3-carboxy-2-hydroxypropane-phosphinic acid derivative, a 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-one, an imidazole analog of mevalonolactone, or a heterocyclic analog of mevalonolactone, a naphthyl analog of mevalonolactone, an octahydro-naphthalene, fluindostatin, a keto analog of lovastatin or a 2,3-di-substituted pyrrole, furan or thiophene.

4. Use according to Claim 2 wherein said HMG CoA reductase inhibitor is pravastatin.

5. Use according to any one of Claims 1 to 4 wherein said angiotensin converting enzyme inhibitor is captopril, zofenopril, enalapril, ceranopril, fosinopril, lisinopril or fentiapril.

6. Use according to any one of Claims 1 to 4 wherein the angiotensin converting enzyme inhibitor is a phosphonate substituted amino or imino acid or salt thereof, a proline derivative, a substituted proline derivative, a mercaptoacyl derivative of a substituted proline, a carboxyalkyl dipeptide derivative, a phosphinylalkanoyl proline derivative or a phosphonamidate derivative.

7. Use according to any one of Claims 1, 2, 4 and 5 wherein the HMG CoA reductase inhibitor is pravastatin and the ACE inhibitor is captopril, fosinopril or ceranopril.

8. Use according to any one of Claims 1 to 7 wherein the mammalian species treated is normotensive.

9. Use according to Claim 8 wherein the pharmaceutical composition prepared for preventing or reducing the risk of a second heart attack in a mammalian species comprises the ACE inhibitor in an amount such that it is administered in an amount below that required to cause hemodynamic effects.

10. Use according to any one of Claims 1 to 9 wherein the composition prepared for preventing or reducing the risk of a second heart attack in a mammalian species comprises a combination of the HMG CoA reductase inhibitor and ACE inhibitor in a weight ratio to each other of within the range of from 0.001:1 to 1000:1.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 10 6104

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X,Y	AM.J.CARDIOL., vol. 68, no. 15, 1991, pages 1436-46, XP000579135 SACKS ET AL.: "Rationale and design of a secondary prevention trial of lowering normal plasma cholesterol levels after acute myocardial infarction: the cholesterol and recurrent event trial (CARE)" * the whole document * ---	1-10	A61K31/365 A61K31/22 A61K31/415 A61K31/66 A61K31/405 A61K31/40
X,Y	BLOOD COAGUL. FIBRINOLYSIS, vol. 4, no. 1, 1993, pages 173-175, XP002011099 SCHMIDT ET AL.: "Elevalted lipoprotein(a) is lowered by a cholesterol synthesis inhibitor in a normocholesterolaemic patient with premature myocardial infaction" * page 173, right-hand column, line 1 - line 3 * * page 174, left-hand column, line 46 - right-hand column, line 3 * * page 174, right-hand column, line 28 - line 33 * * page 175, left-hand column, line 1 - line 18 * ---	1-10	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
X,Y, P	AM.J.CARDIOL., vol. 76, no. 9, 28 September 1995, pages 98c-106c, XP000579209 PFEFFER ET AL.: "Choilesterol and recurrent events: a secondary prevention trial for normolipidemic patients" * the whole document * ---	1-10	
Y,D	EP-A-0 461 548 (E.R.SQUIBB & SONS) * claims 1-20 * -----	1-10	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	19 August 1996	Gerli, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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